

Exhibit A

Reproducibility of Relaxation Times and Spin Density Calculated from Routine MR Imaging Sequences: Clinical Study of the CNS

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This study was undertaken to determine if routine clinical magnetic resonance imaging sequences using only two different repetition times (TRs) and with only two sequential spin echoes (SEs) can be used to calculate reproducible relaxation time and spin density values for normal central nervous system tissue using a 0.35 T production-model instrument. In 43 patients 650 regions of interest of 11 different anatomic sites were measured. T1 and T2 relaxation times and spin density were measured. For each anatomic location, the mean and standard deviation of these values were determined. In most solid regions of brain, the standard deviation of both T1 and T2 was 4%–8%. Relaxation times of cortical gray matter varied more, with a standard deviation of 10%, probably because of volume-averaging with adjacent cerebrospinal fluid (CSF). CSF and ocular vitreous humor were neither reproducibly nor accurately measured because of the short TR and TE settings of the imaging sequences relative to the long T1 and T2 relaxation times of these substances. Significant and reproducible differences were found between the spin densities of gray matter and white matter, as well as between different regions of white matter. These differences are of major importance in contrast discrimination of gray and white matter on the long TR images. Knowing that relaxation values and spin densities calculated from routine imaging sequences are in fact reproducible, these normal ranges can now be used to investigate changes occurring in disease states.

Detection of pathology with magnetic resonance (MR) imaging depends not only on optimal depiction of normal and abnormal anatomy but also on the detection of differences in signal intensity between distinct tissue subtypes even before anatomic derangement occurs. While the absolute or relative intensity of a region is affected by different machine settings, the T1 and T2 relaxation time and the resonating proton density of distinct regions are unaffected. Therefore, quantification of T1 and T2 relaxation times and of spin density has been suggested as a fundamental way of characterizing tissue. Knowledge of the range of normal for the relaxation times (at any given field strength) of various organs in vivo is vital for a thorough understanding of disease processes as well as for choosing the optimal imaging sequence to best demonstrate pathology. Subtle processes diffusely affecting the brain may not be visible on intensity images as an obvious abnormality, but may still be detectable if significant alteration of T1 or T2 relaxation values occurs. Knowledge of the normal T1 and T2 values and their variation would be essential for making such diagnoses. This report discusses the reproducibility of T1, T2, and resonating proton density data for normal central nervous system (CNS) structures calculated from routine brain MR imaging sequences at 0.35 T using a production-model instrument.

Subjects and Methods

In 43 patients undergoing MR imaging of the brain, 650 regions of interest (ROIs) were obtained of 11 different normal anatomic structures. The intensities, the calculated T1 and

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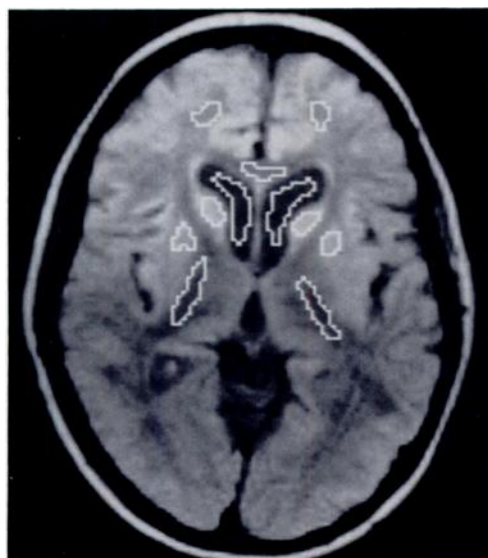


Fig. 1.—Example of how normal ROIs were obtained. White and gray matter in frontal region is more intense secondary to receiver coil proximity. Posterior limb of internal capsule is less intense than subcortical white matter secondary to lower spin density.

T2 relaxation times, and the relative resonating hydrogen densities were measured (fig. 1).

The patients were chosen on the basis of being imaged with spin-echo (SE) sequences using two different repetition times (TRs), making calculation of T1 relaxation times possible. Studies with motion artifacts or registration errors between the imaging sequences were excluded. Several of the patients had a focal abnormality at a site well away from the measured normal ROIs. None of the patients had diffuse brain pathology (such as encephalitis, global ischemia, etc.) or radiation therapy that might affect the entire brain. The patients were 11–79 years old; only two were younger than 19.

The patients were imaged with an MR imager using a superconducting magnet operating at 0.35 T (Diasonics MT/S). The patients were imaged in a 25 cm head coil. A simultaneous multiple-slice SE technique was used with two SE samplings (at 28 and 56 msec) of each slice. Four signal acquisitions were averaged for each pulse sequence. Two sequences of different TR settings were obtained in all selected patients. Thirty-three patients had 500/2000 msec TR sequence settings; nine had 500/1500 msec; and one had 1000/2000 msec. Forty-one patients were imaged in the axial plane and six in the coronal plane. The patients' position was varied slightly within the head coil to center the studies about areas of known pathology. Therefore, potential variations secondary to position within the head coil were at least partly canceled out.

Eleven different anatomic regions were measured including the cortical gray matter, subcortical white matter, head of the caudate nucleus, posterior limb of the internal capsule, lenticular nucleus, pulvinar of the thalamus, cerebellar gray and white matter, orbital fat, ocular vitreous humor, and intraventricular cerebrospinal fluid (CSF). The subcortical white matter was subdivided into frontal, parietal, temporal, and occipital regions. The cortical gray matter was similarly subdivided, with the addition of insular cortex. The ROIs were carefully chosen to minimize the effects of volume averaging. The number of pixels within each ROI was recorded, with a minimum of five pixels for each ROI.

For each region the mean intensity and standard deviation (SD) of the intensity was measured on the four images at that level (based on two TR sequences each with two echo times [TEs]). Using these mean intensity values, the T1 and T2 relaxation times and relative hydrogen density values were calculated using the SE equation for two SEs:

$$I = k(N[H]) (1 - 2e^{-(TR - 3TE)/T1} + 2e^{-(TR - TE)/T1} - \exp^{-TR/T1})e^{-TE/T2}. \quad (1)$$

On our imager, T1 and 3T1 settings are 14 and 42 msec, respectively, thereby resulting in SE times of 28 and 56 msec. The T1 values of the ROIs were calculated using an iterative technique using the intensities of the first echoes (28 msec TE) of the two different TR sequences. Separate T2 values were calculated for both TR sequences using the first and second echoes from each TR. Finally, a relative spin density value $k(N[H])$ was calculated based on the T1 value obtained from the first echo of each TR sequence and the mean T2 value.

Previous articles from this institution have used a simplified form of equation 1 [1–3]:

$$I = k(N[H]) (1 - e^{-TR/T1})e^{-TE/T2}. \quad (2)$$

This simplified equation does not consider the effect of the dual 180° sampling pulses on the longitudinal component of magnetization. The more complex equation represents a significantly more accurate relation between the tissue parameters and instrument settings as reflected in resultant signal intensity than that of the simple equation [4].

The means and standard deviations of the calculated T1 and T2 values for each of the distinct anatomic locations were determined in three different ways. First, all of the individual ROIs were subdivided by anatomic location, and the mean relaxation times and SDs were determined for each anatomic location. This method equally weights the individual ROIs in calculating the mean values. Patients in whom more ROIs were obtained will contribute more to this mean and SD. For example, a study in which 10 subcortical white-matter ROIs were obtained would influence the white-matter mean relaxation times more than a study with only two white-matter ROIs.

Second, the different relaxation time measurements for each anatomic region within an individual study were averaged or pooled, and these means were then averaged among different patients to yield a mean value and SD of the pooled measurements. For example, the 10 subcortical white-matter ROIs within one patient study were averaged to obtain mean relaxation times for subcortical white matter for that patient. This was done for each patient, and these means were then averaged to obtain a mean and SD of the pooled white-matter relaxation time measurements. In this method, each individual patient (instead of each individual ROI) is equally weighted in calculating the mean value of the pooled measurements. The SD of these means should be less than that calculated when equally weighting the individual ROIs. The SD obtained from weighting each ROI equally would be used when analyzing an individual ROI measurement because of the greater inherent inaccuracy in a single measurement. The SD of the pooled measurements value would be useful in evaluating the variability of T1 or T2 relaxation times in which several ROIs on the same anatomic region within the same patient had been obtained, for example, cases of diffuse CNS disease.

Third, similar normal regions on each side of the midline were obtained within the same slice of the same patient. For these pairs of comparable left-right regions, the percentage difference of T1 and T2 values and the SD of the percentage difference were measured for each anatomic region. This variation would play a role in determining if a region is abnormal by comparing it with the contralateral side.

TABLE 1: Mean T1 and T2 Relaxation Times of Distinct Anatomic Regions of the Brain

Region	Mean Relaxation Time in msec (SD)		No. of ROIs	No. Pixels/ ROI (average)
	T1	T2		
Cortical gray matter	701.5 (67.8)	60.0 (4.7)	152	15
Caudate head	655.2 (35.0)	58.6 (3.7)	29	15
Cerebellar gray matter	651.8 (46.0)	59.8 (3.5)	44	48
Subcortical white matter	419.3 (33.5)	53.1 (4.1)	152	19
Posterior internal capsule	439.0 (22.3)	53.7 (3.6)	27	28
Cerebellar white matter	455.6 (37.8)	56.8 (3.8)	38	27
Orbital fat	290.1 (35.6)	57.3 (3.4)	47	13
Ocular vitreous	2799.7 (426.4)	159.7 (91.5)	42	27
Cerebrospinal fluid	2719.6 (405.7)	166.3 (74.5)	52	44
Lenticular nucleus	600.2 (40.8)	55.6 (2.7)	16	25
Thalamus	609.5 (34.9)	55.5 (2.1)	8	23

Note.—The mean T2 was calculated using both TR sequence pairs. ROI = region of interest.

In addition, the variability between different regions of subcortical white matter was measured. The variation in T1 relaxation times of subcortical white-matter ROIs using different TR pairs was also measured.

It is important to emphasize that the calculated relative hydrogen density, $k(N[H])$ in equation 1, represents a relative value of resonating hydrogen density within a single study. Without normalizing these values to a standard or to a particular anatomic structure, these relative hydrogen density values can only be compared with values from other ROIs within the same study. In this study we calculated the relative hydrogen densities of cortical gray, caudate, thalamus, and subcortical white matter by normalizing the hydrogen densities of these structures to that of subcortical white matter within the same patient. The relative hydrogen densities of cerebellar gray and white matter were also measured. The normalized spin densities of the different patients were averaged.

Results

Mean Values

The mean T1 and T2 relaxation times of the chosen normal tissues are shown in table 1. As stated in the methods section, patients in whom normal ROIs were analyzed included those with focal lesions well removed from the site of measured normal tissue. The data were initially analyzed to evaluate the possibility that such normal tissue in patients with distant focal CNS lesions might have different relaxation times than those of patients without CNS disease. The 41 adult patients were subdivided into two groups: 29 with and 12 without known CNS disease. The mean T1 and T2 relaxation times for each anatomic location did not vary significantly between the two groups. Thus, the relaxation times of the normal areas distant to the patients' focal abnormalities were not significantly different than the relaxation times of similar locations measured from patients without known CNS disease. Incidentally, although no significant relations were found between patient age and relaxation times, insufficient age-range data were available to adequately address this question.

The mean relaxation times of any given anatomic region, whether calculated by considering each ROI individually or calculated by taking the average of the mean values for each patient, differed by less than 1%. The mean calculated T1

and T2 values of cortical gray matter were 701 and 61 msec, respectively. The T2 value of the head of the caudate and the cerebellar gray matter did not differ significantly from that of the cortical gray matter; however, the T1 value of the two regions was 652 msec for cerebellar gray and 655 msec for caudate. For subcortical white matter both T1 and T2 values were significantly shorter, with a T1 of 419 msec and a T2 of 53 msec. The posterior limb of the internal capsule had a T2 value not significantly different from that of subcortical white matter, but it had a slightly longer T1 of 439 msec. The cerebellar white matter, with a T1 of 453 msec and a T2 of 58 msec, had slightly longer relaxation times than subcortical white matter.

Variability

The variability in relaxation times as calculated in multiple ways is shown in table 2. Ocular vitreous humor and CSF are discussed below and will not be considered here. First, by equally weighting the individual ROIs, all of the regions except for cortical gray matter had SDs ($SD/mean \times 100$) of 3%–8% for both T1 and T2 values. For cortical gray matter this SD was about 10%.

The SD of the pooled measurements would be expected to be less than the variation of individual measurements because it represents a mean of means. This was generally the case, as shown in table 1.

The previous two measures of variance represent variation between patients, that is, interpatient variation. The data were also analyzed for variation within an individual patient, intrapatient variation, by measuring the variation between comparable regions on the left and right of midline. This left-right variation for T2 relaxation times was less than the variance of the ROIs considered individually for all of the different anatomic locations. For T1 values, the left-right variation was less for all locations except cortical gray matter and internal capsule. The SD of the T1 of the internal capsule was only about 5% for both left-right pairs and for all of the individual measurements.

The data were also analyzed to see whether the position of interest in the head coil had any effect on the calculated

TABLE 2: Variations in Standard Deviations of Mean Relaxation Times Based on Method of Determination

Region	Mean T1 (msec)	% SD of T1			Mean T2 (msec)	% SD of T2		
		Indi- vidual ROIs	Pooled	L-R		Indi- vidual ROIs	Pooled	L-R
Cortical gray matter	701.5	9.7	4.6	10.5	60.0	7.9	5.4	7.2
Caudate head	655.2	5.4	4.5	3.4	58.6	6.4	5.1	4.9
Cerebellar gray matter	651.8	7.0	6.8	4.9	59.8	5.8	5.7	4.9
Subcortical white matter	419.3	8.0	6.6	7.5	53.1	7.6	5.2	6.2
Posterior internal capsule	439.0	5.1	4.4	5.1	53.7	6.8	5.8	4.0
Cerebellar white matter	455.6	8.3	8.9	3.8	56.8	6.7	6.4	4.3
Orbital fat	290.1	12.3	10.9	12.2	57.3	5.9	4.9	4.2
Ocular vitreous	2799.7	15.2	159.7	54.9	44.7	25.8
Cerebrospinal fluid	2719.6	14.9	166.3	43.4	29.7	31.0
Lenticular nucleus	600.2	6.8	55.6	4.9
Thalamus	609.5	5.7	55.5	3.8

Note.—Mean T2 was calculated using both TR sequence pairs. SDs based on individual regions of interest (ROIs) were calculated by weighting each ROI equally; SDs based on pooled measurements were calculated by weighting each run equally; left (L)-right (R) SDs represent variations between comparable regions on the left and right of midline within the same study and same slice.

TABLE 3: Subcortical White-Matter Relaxation Rates in Different Locations on Axial MR Images

Region of Subcortical White Matter	T1		T2	
	Average Time in msec (SD)	No. of ROIs	Average Time in msec (SD)	No. of ROIs
All	414 (33)	115	53.9 (4.4)	114
Frontal	412 (38)	43	54.3 (3.8)	43
Parietotemporal	417 (33)	25	53.5 (4.5)	25
Occipital	416 (30)	29	54.5 (5.3)	28

Note.—Long TRs were used (1500 and 2000 msec). ROI = region of interest.

T1 or T2 values. This was done by comparing the different subdivisions of subcortical white matter. More specifically the subcortical white matter ROIs were subdivided into frontal, parietotemporal, and occipital regions on the axial sections. The relaxation times of these subcategories were compared, and no significant differences were found in their T1 or T2 values (table 3). Very little variation was seen between white matter in different locations. However, if intensities of these different white-matter ROIs within a section of a study are compared, the variation is much larger. The regions closer to the receiver coils were significantly more intense because of improved signal detection. On the axial images, the frontal and occipital subcortical white matter regions were more intense than the parietotemporal regions. However, since this effect was equally present on all four SE images of one level, this does not significantly affect the calculations of T1 and T2 because the intensity variations were canceled out in the calculations.

Dependence on Machine Parameters

The calculated T1 and T2 relaxation times of the normal regions were compared between studies using TR sequence pairs of 500/2000 msec and those studies using TR settings of 500/1500 msec. The mean T1 and T2 values for gray

matter and white matter did not significantly differ between these two sequence pairs. In passing, it should be stated that if the T1 relaxation times were calculated for the 500/2000 msec TR sequence pair using the previously reported simplified equation (equation 2), then the mean T1 value for cortical gray matter would be 820 msec rather than 701 msec, and the mean T1 for white matter would be 477 msec rather than 419. Also, the mean T1 value obtained from the 500/1500 msec TR sequence pair for gray matter would be artifactually higher than that obtained from the 500/2000 msec TR sequence pair by about 25 msec.

Calculated T1 values of subcortical white matter tended to be longer in the coronal imaging plane. The reason is unclear. Insufficient measurements were made of studies in the coronal imaging plane to verify this initial observation, and it is currently being investigated. The inclusion of these cases in our data base does not significantly alter the mean values and SDs.

T2 values did not vary significantly when different TRs were used for the calculation.

Ocular Vitreous Humor and CSF

Calculated relaxation times of CSF and ocular vitreous humor using intensity measurements obtained from normal imaging sequences were neither consistent nor accurate. Both of these substances are fluids with significantly longer T1 and T2 values than the other regions analyzed. The calculation of T1 relaxation times in fluids using only two TR settings often leads to spuriously high values of T1. If the calculated T1 value was greater than 3000 msec then it was automatically set at 3000 msec. Thus, the SD of the T1 values for CSF and ocular vitreous humor are not meaningful. The mean T1 values of CSF and vitreous humor were 2800 and 2700 msec, respectively, which are very long compared with our long TR of 2000 msec. Similarly, the mean T2 relaxation times of CSF and vitreous humor were 187 and 148 msec, respectively, which are also long compared with our SE times of 28 and 56 msec. The SDs of both the T1 and T2 relaxation

TABLE 4: Relative Hydrogen Densities of Several Normal Central Nervous System Structures

Region	Hydrogen Density		Counts
	Mean (SD) [%SD]	Range	
Cortical gray matter . . .	123.9 (6.7) [5.4]	114.1–139.3	27
Internal capsule	89.9 (2.9) [3.2]	84.9–96.8	11
Caudate head	120.1 (6.2) [5.2]	109.9–130.7	13
Cerebellar gray matter . .	122.6 (3.5) [2.9]	117.2–129.4	17

Note.—Hydrogen densities of subcortical white matter and cerebellar white matter have been set to 100 and the measurements are relative to this value. Results for each separate run are pooled so the "count" represents the number of runs rather than the number of regions of interest (ROIs).

times of CSF and ocular vitreous humor were much larger than for all of the other anatomic regions.

The T2 values of CSF and ocular vitreous calculated from the short TR sequence were often grossly inaccurate. In these substances with long T1 relaxation values there was very low signal intensity in the short TR sequence secondary to insufficient time for longitudinal remagnetization. With this low signal intensity of fluids, noise has a significant adverse effect on the T2 calculation. This is illustrated by the fact that the percentage difference of the T2 values calculated from the long versus the short TR sequences was much greater for CSF and ocular vitreous humor than for all other regions. This large difference was secondary to several obviously spurious high T2 values calculated for the 500 msec TR sequence. Long TR sequences are therefore superior for calculating the T2 relaxation times of CSF and ocular vitreous humor.

Hydrogen Density

The calculated relative hydrogen density values represent the product of the real hydrogen density and a constant, k , that varies from study to study (see equation 1). The relative hydrogen density between two regions, however, can be compared between different studies by either normalizing to a standard or to a normal anatomic region. Shown in table 4 are the hydrogen densities of cortical gray matter, caudate, and internal capsule divided by that of subcortical white matter. Also shown is the cerebellar gray hydrogen density compared with cerebellar white matter. Note the calculated hydrogen densities of gray matter and caudate are 24% and 20% higher, respectively, than that of white matter. Similarly, cerebellar gray has a higher hydrogen density than cerebellar white matter by about 23%. This difference in spin density between gray and white matter is the major determinant in the differential intensity of gray and white matter on the 2000 msec TR sequence—especially on the first echo. Of interest, the measured hydrogen density of the posterior limb of the internal capsule is 10% less than that of subcortical white matter. On studies with TR settings of 2000 msec, the internal capsule has a lower signal intensity than subcortical white matter (fig. 1). The T1 and T2 relaxation times of these two regions are similar; therefore, the lower signal intensity of the internal capsule is secondary to lower resonating proton density. All of these differences in relative hydrogen are statistically significant and are quite reproducible with an SD of only 3%–5%.

Discussion

Evaluation of the reproducibility of MR imaging measurements is fundamentally different from that of computed tomography (CT). Unlike CT, where the attenuation of a voxel is directly related to its physical density, the signal intensity on MR imaging is multiparametric and dependent on T1 and T2 relaxation times, hydrogen density, motion, and instrumental parameters such as TE, TR, and the type of pulse sequence. Also, proximity to the receiver coil plays a role. Therefore, absolute intensity is useless in evaluating normality of a given tissue. Visually comparing the intensity from one region with another is the usual way of detecting abnormality. Establishing ranges of normal using relative intensities is possible but cumbersome, since two regions must be measured each time and the relative intensity between two regions will vary depending on the imaging sequence used. The obvious choice for tissue characterization on a nonspectroscopic MR imager is based on the primary determinants of signal intensity: T1 and T2 relaxation times, resonating hydrogen density, and motion. Although a factor in thoracic and abdominal imaging, motion is not a major factor in imaging solid brain tissue.

For our routine imaging of the brain, we usually obtain two sequences with TR settings of 500 and 2000 msec. Only two TR values are used to calculate the T1 relaxation times and only two TE values are used to calculate T2 relaxation times. Based on phantom studies described in an accompanying report [5], we know that our routine TR pair of 500 and 2000 msec is optimal for calculating the T1 of any brain tissue that falls within a T1 range of 300–900 msec. The two echo samplings at 28 and 56 msec are also suitably timed to measure the T2 relaxation of brain, which normally is 50–60 msec for our imager. Use of additional TR settings or SE samplings in our imaging routine may improve the reproducibility of our relaxation time and hydrogen density calculations. However, this would cause a significant increase in patient examination time and probably is not necessary, since for most tissues in the brain, the measured values are in fact reproducible and independent of imaging sequence. The SD of less than 8% is sufficient to reliably distinguish different normal anatomic regions as well as provide limits for normal in borderline cases. Of note, this variation is larger than the T1 and T2 relaxation time variation found in the phantom study. Perhaps the increased variation is secondary to physiologic differences in the actual T1 and T2 relaxation times in structures of different patients. Cortical gray relaxation time measurements were probably less reproducible because of the narrow dimensions of cortical gray matter, as well as its proximity to CSF, which has very different relaxation characteristics. Volume-averaging of CSF is therefore difficult to avoid. The larger variation may also be partly secondary to volume-averaging of the numerous vascular structures lying next to the cerebral cortex. These explanations for the larger variability in cortical gray relaxation times may also be responsible for the fact that our measured T1 value of cortical gray matter of 700 msec was larger than that of basal ganglia and cerebellar gray, which were about 650 msec.

As with the phantom part of our study [5], there were no significant increases or decreases in relaxation time variability

between left and right, slice to slice, or between different studies.

An interesting finding was the significant difference in spin densities between gray and white matter as well as between internal capsule and subcortical white matter. While the absolute hydrogen concentration in these different tissues varies by less than 0.1% [6], the MR signal reflects the resonating protons only. Chemical-shift imaging indicates that signal from normal brain imaging is almost solely from water protons, with negligible signal originating from lipid protons [7]. The abundant protons bound to the myelinated white matter have a very short T2 and do not give off a measurable signal. Thus, although white matter has an absolute proton density similar to gray matter, a larger portion of them are myelin-bound and do not contribute to the MR signal. Hence, the spin density of white matter is lower.

In summary, the T1 and T2 relaxation times and the relative proton density can be measured reproducibly using a clinical imager. The variation of individual T1 or T2 relaxation time measurements for normal solid CNS is 4%–8%. Phantom studies have determined that about 2%–4% of this variation can be ascribed to instrument variation [5]. It may be that physiologic differences explain the rest. The calculated T1 values are not significantly affected by whether a 500/2000 or 500/1500 msec TR pair is used. The T2 values obtained from sequences with different TR settings are not significantly different. As expected, measurement of the relaxation times of liquid CSF or ocular vitreous humor are neither very reproducible nor accurate because of the imaging sequences used. Finally, significant and reproducible differences were found in

the resonating proton densities between gray matter and different regions of white matter. Our results are now being used to evaluate the significance of changes in T1 and T2 relaxation times and in resonating proton density occurring in various disease states.

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